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Review

Local adipose tissue depots as cardiovascular risk factors

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Abstract

Obesity is associated with increased cardiovascular morbidity and mortality. Although obesity-associated hypertension, dyslipidemia and insulin resistance account in part for this association, it becomes increasingly apparent that a systemic and local pro-inflammatory response of adipose tissue might also be a contributing factor.

White adipose tissue (WAT) is a highly active organ secreting various peptides such as cytokines, chemokines and hormone-like proteins. Besides the visceral and subcutaneous depots, WAT is also found in the close vicinity of blood vessels (perivascular adipose tissue), where it secretes cytokines such as interleukin-1, tumor necrosis factor α , pro-atherogenic chemokines, and pro-angiogenic peptides. These factors appear to contribute directly to alterations of the function and structure of the vascular wall, including chronic inflammation, alterations of vascular tone, proliferation of smooth muscle cells, neo-angiogenesis and hence to the development of atherosclerosis and cardiovascular complications.

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Keywords: Atherosclerosis; White adipose tissue; Cytokines; Chemokines; Obesity; Cardiovascular risk; Angiogenesis

1. Introduction

In the developed world, obesity and the associated metabolic and cardiovascular complication is a major public health problem and one of the major contributors to premature death [1]. In Europe, the prevalence of obesity has tripled since the 1980s, and it has been estimated that over 4 million people become obese every year [2]. Recent data from the Centers for Disease Control and Prevention predict that the prevalence of diabetes in the USA will double by 2050 and will affect over 48 million people (or 12% of the population), which is mostly a direct consequence of the increase in overweight and obesity [3]. Moreover, the obesity pandemic is now reaching hitherto spared regions of the world, such as Southeast Asia, the Indian subcontinent and even Africa [4].

Obesity reflects the accumulation of triglycerides in fat deposits, leading to adipocyte hypertrophy and hyperplasia.

In evolutionary terms, fat deposits serve as caloric depots in case of food deprivation. However, once an advantage in the times when we were hunters and gatherers, the machinery leading to the efficient accumulation of fat stores has become deleterious. Excess white adipose tissue (WAT), leading to overweight (BMI 25–30) and obesity (BMI >30), has an impact on virtually all organ systems, including cardiovascular (endothelial dysfunction, coronary heart disease, hypertension, congestive heart failure), respiratory (obstructive sleep apnoea, hypoventilation), gastro-intestinal (gall-bladder stones, obesity-associated gastroesophageal reflux disease), metabolic (insulin resistance, development of type 2 diabetes, hypercholesterolemia), urinary (hyperfiltration, microalbuminuria), oncologic (increased incidence of breast, endometrial and colon cancer) as well as the osteoarticular system (osteoarthritis) [5–9].

Since the discovery over a decade ago that WAT secretes various metabolically active molecules, such as tumor necrosis factor α (TNF α) and leptin, our view of adipose tissue being an inert fat storage organ has changed to that of a tissue secreting dozens, if not hundreds, of biologically active compounds,

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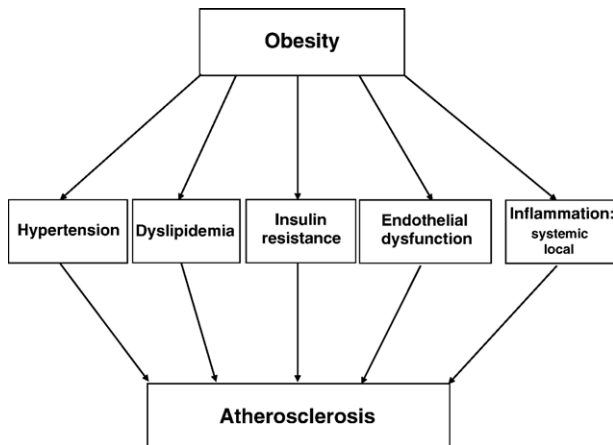


Fig. 1. Relation between obesity and the development of atherosclerosis. Obesity has been associated with hypertension, dyslipidemia, insulin resistance, endothelial dysfunction and inflammation, which all have been linked to atherosclerosis.

which are implicated in the regulation of food intake, inflammation and angiogenesis, either through systemic or local paracrine effects, ultimately resulting in a chronic low grade inflammatory state [10,11]. Hence, obesity per se is now considered as a cardiovascular risk factor contributing in the development of atherosclerosis independently of hypertension, dyslipidemia and diabetes (Fig. 1) [12].

Atherosclerosis represents a heterogeneous disease of multiple different causes. Since it can be considered as a chronic inflammatory state characterized by the accumulation of leukocytes, the proliferation of smooth muscle cells and neo-angiogenesis within the vascular wall, it is appealing

to speculate that specific localised adipose tissue depots, such as perivascular WAT (pWAT), contribute to obesity-associated atherosclerosis [13]. The present review focuses on our current knowledge of the distribution, regulation and secretory activity of pWAT.

2. WAT as a secretory organ

WAT secretes cytokines, chemokines and hormone-like proteins. These peptides can be subdivided according to their principal effects into molecules acting principally on metabolic processes (such as the regulation of food intake and body weight, and insulin sensitivity), and in factors modulating inflammation [14]. The WAT-derived factors can also be categorized according to their range of action, which can be local through the creation of concentration gradients (paracrine), or systemic (endocrine) (Fig. 2).

2.1. Cytokines

Cytokines are peptides produced in response to certain stimulation, which are bioactive at very low levels and play an integral role in the regulation inflammation, immunity, cell growth and maturation. Over 100 cytokines have been described and they have been classified as interleukins, interferons, chemokines, haematopoietic factors and growth factors. They are produced by cells of the haematopoietic lineage, including macrophages, T-cells, B-cells and natural killer cells, but also by non-haematopoietic cells, such as hepatocytes, epithelial cells and fibroblasts [15]. Several cytokines, such as interleukin-1 (IL-1), interleukin-1 receptor antagonist (IL-1Ra), interleukin-6 (IL-6), transforming

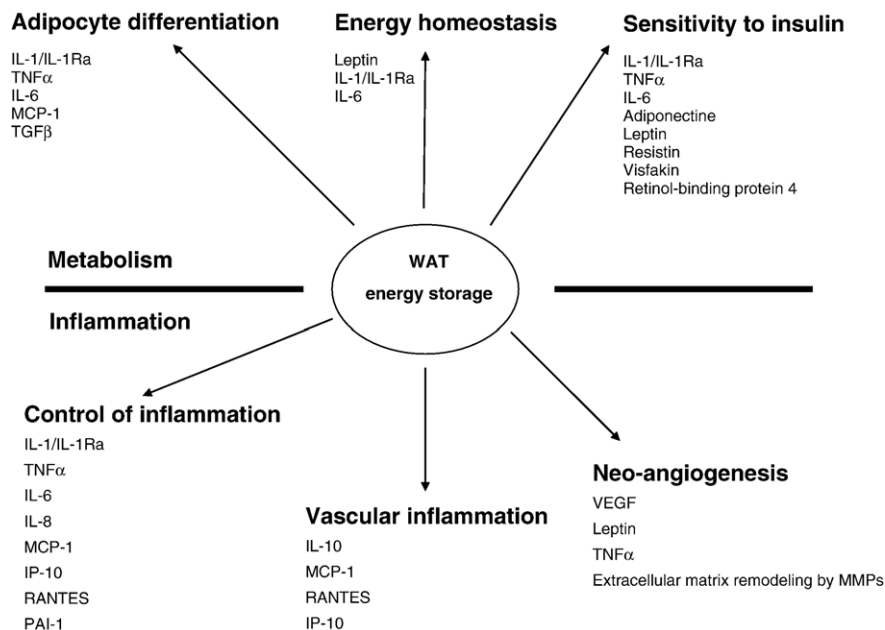


Fig. 2. White adipose tissue is a highly active organ secreting various peptides implicated in inflammatory and metabolic processes, either by paracrine effect or endocrine/systemic effect.

growth factor β (TGF β), TNF α and certain chemokines are also produced by WAT as will be discussed in detail below.

2.2. Chemokines

Chemokines are small secreted basic proteins, classified into four subclasses according to the position of the cysteine residue (i.e. CXC, C, CX3C and CC) [16]. They are implicated in the chemoattraction of inflammatory cells through generation of local concentration gradients, acting essentially through paracrine effects [10]. Therefore, the action of these factors is often related to the proximity of the secreting tissue (e.g. adipose tissue) to the target tissue, such as leukocytes or the vascular wall. Through their capacity to recruit and activate cells, chemokines are involved in multiple systemic inflammatory disorders, such as rheumatoid arthritis, glomerulonephritis and atherosclerosis [17]. The production of chemokines is induced by various stimuli, such as vascular injury, oxidized lipids, growth factors and cytokines [10,16]. In the often diabetic obese patient, glycated and oxidized lipids (advanced glycation end products) also contribute to augmented cytokines production [18], therefore further accelerating atherosclerosis.

2.3. Other proteins and peptides

One of the major proteins derived from WAT is adiponectin (or also called AdipoQ, Acrp30, ApM1 or GPB28) which is the most abundant adipose-derived protein in the circulation (5–30 $\mu\text{g/ml}$), accounting for 0.01% of total plasma protein [19–21]. Adiponectin plays a role in the maintenance of insulin sensibility, and its decline observed in obesity has been linked to type 2 diabetes [22]. Moreover, the overexpression of adiponectine in leptin-deficient ob/ob mice improves insulin sensitivity [23]. Besides regulating insulin sensitivity, adiponectin has also anti-atherosclerotic effects by inhibiting proliferation of smooth muscle cells, one of the hallmarks of atherosclerosis [24], as well as by increasing inhibitors of metalloproteinases, which are necessary for the degradation of extracellular matrix including the fibrous cap on atherosclerotic plaques) and neo-angiogenesis [25].

In contrast, resistin, which is another peptide secreted by monocytes and WAT, is increased in type 2 diabetes and some studies have shown a correlation between plasma resistin levels, body mass index and adiposity [26]. However, the secretion of resistin by human WAT is a matter of some debate [27]. The administration of resistin induces insulin resistance in euglycemic, hyperinsulinemic conditions in rodents, although these findings have also been controversial [28,29]. Finally, resistin could also have inflammatory properties, as it induces the expression of adhesion molecules on endothelial cells [30].

A more recently discovered peptide is visfatin, which is derived from visceral adipose tissue [31]. Visfatin decreases plasma glucose levels, and its actions have therefore been described as insulin mimetic. Like insulin, visfatin induces

phosphorylation of signal proteins downstream the insulin receptor, improving insulin sensitivity and representing a potential defence mechanism against obesity-induced insulin resistance [32]. Recently, retinol-binding protein-4 (RBP4), a new adipokine which acts as transport molecule for retinol (vitamine A), was reported to be linked to impaired glucose tolerance and type 2 diabetes, and was found to be correlated with body mass index [33,34]. Moreover, in a murine model, reduction of plasma RBP4 improved insulin resistance [35].

Leptin has been much investigated over the past decade as an appetite-regulating factor. It is a circulating protein produced by adipose tissue with central and peripheral actions on metabolic and inflammatory processes. Typically, leptin controls food intake and energy expenditure through hypothalamic pathways, thereby contributing to glucose homeostasis. However, it seems that leptin also has several immunomodulatory actions, as it regulates the secretion of chemokines and cytokines in monocytes [36].

The pro-atherogenic plasminogen activator inhibitor-1 (PAI-1) inhibits the breakdown of fibrin clots, thereby enhancing the formation of thrombi upon rupture of plaques; moreover, it contributes to vascular wall remodelling by altering the fibrinolytic balance [37,38]. Elevated plasma levels of PAI-1 are found in obesity and it has hence been suspected to represent one of the mediators of the obesity-associated excess cardiovascular risk [39].

3. Localized WAT compartments

In humans, the development of obesity leads not only to an increase in fat depots in classical locations, such as in the subcutaneous and intra-abdominal (or visceral) compartment, but also around specific organs, such as the heart (epicardial), blood vessels (perivascular) and the kidney (renal), which have all been described as locations for ectopic fat storage [40] (Table 1). It has been demonstrated in a rabbit model of obesity that fat depots occur in various locations, such as in the neck, retroperitoneal space, mesenterium, mediastinum, renal sinus and around blood vessels [41]. Organ function may be altered by surrounding fat deposits, as they may compress the adjacent organ, thereby mechanically impairing its function. On the other hand, local fat depots could also impact on the surrounding structures through secreted factors, such as chemokines and cytokines.

3.1. Visceral WAT

Visceral WAT consists of fat deposits around anatomic structures located in the retroperitoneal, omental and mesenteric spaces. Many studies support a detrimental effect of intra-abdominal fat on metabolism and cardiovascular risk [42], although the mechanisms of action remain largely speculative. Increased visceral WAT is a risk factor for dyslipidemia, insulin resistance, diabetes, and hypertension. Visceral adiposity is estimated by the measurement of waist

Table 1

Besides its localization in subcutaneous tissue, specific organ-associated WAT depots exist (see text for details)

WAT localisation	Local factors		Putative consequences
Kidney	Na ⁺ reabsorption		Increased intravascular volume hypertension
Muscle	Secretion of	TNF α IL-6 Free fatty acids	Insulin resistance
Visceral	Secretion of	IL-8 MCP-1 IP-10 RANTES	Local and systemic inflammation
Epicardial	Secretion of	IL-6 IL-1 β MCP-1 TNF α	Local inflammation and chemotaxis
Perivascular	Secretion of	MCP-1 IL-1/IL-1Ra IL-6 IL-8 IP-10 RANTES TNF α	Atherosclerosis systolic hypertension
	Increased vascular tonus		

circumference, which has been included in the definition of the metabolic syndrome [43]. However, these measurements are quite imprecise and may not reflect the actual amount of visceral fat [44]. The best tools to estimate the amount of visceral fat include imaging with computer tomography (CT) or magnetic resonance imaging (MRI). Recently, it has been shown that a good correlation exists between visceral adipose tissue and epicardial fat measured by echography, therefore representing an easier tool for the estimation of visceral fat mass for clinical studies [45].

3.2. Ectopic fat storage in muscle

Ectopic lipid storage in muscle has been first described in 1967 [46]. In Indian non-diabetic Pima men, an ethnic group with a pronounced tendency to obesity and type 2 diabetes, increased muscle triglyceride content was associated with insulin resistance and type 2 diabetes [47]. However, increased lipid contents of muscle were found to be predominately intracellular. Consistent with this, Goodpaster et al. found that the muscular triglycerides in obese type 2 diabetics was located within the myocytes [48]. New data suggest that extracellular muscular fat also contributes to muscle insulin resistance, as fat deposits located beneath the fascia lata in the thigh are associated with insulin resistance in obesity [49]. Mechanistically, it is plausible that adipocytes located around muscle cells produce high local concentrations of cytokines, such as TNF α or IL-6, which are all known to alter insulin sensitivity [50,51]. Alterna-

tively, free fatty acids from adipose tissue may interact negatively with normal insulin sensitivity [52].

3.3. Ectopic fat storage in kidney

In animal models of diet-induced obesity, intrarenal fat deposits can directly or indirectly alter renal structure [40]. For instance, diet-induced obesity in dogs and rabbits is associated with larger kidneys and increased fat deposits in the renal sinus [53]. Consequently, renal veins and lymphatic outflow are constricted, resulting in augmentation of renal interstitial fluid pressure and prolongation of sodium transit time, leading to a significant resorption. This has been proposed to contribute to the obesity-induced hypertension observed in animals and humans [54]. However, other mechanisms have been implicated as well, such as increased renal sympathetic activity, activation of the renin-angiotensin-aldosterone system and a direct sodium retention effect by hyperinsulinemia [55].

3.4. Epicardial adipose tissue

Obesity predisposes to the accumulation of excess epicardial fat [40], which shares with intra-abdominal fat the capacity to secrete cytokines [56]. Its quantity, as measured by echography, has been well correlated with the mass of visceral adipose tissue measured by magnetic resonance imaging [45]. Consistent with this hypothesis, a recent study showed that epicardial adipose tissue represents a novel indicator of cardiovascular risk [57]. Human epicardial adipose tissue has considerable secretory activity; for instance, epicardial adipose tissue from patients undergoing elective coronary aortic by-pass grafting contained significantly more mRNA and protein for IL-1 β , IL-6, monocyte chemoattractant protein 1 (MCP-1) and TNF α compared to subcutaneous adipose tissue [58]. In keeping with this finding, the cytokine concentrations in epicardial fat was correlated with an accumulation of inflammatory cells, such as T-lymphocytes, macrophages and mast cells, in the vicinity of epicardial adipose tissue. In another study, epicardial mRNA levels for CD45, a marker of macrophage infiltration, was significantly increased compared to abdominal fat [56]. Consistent with this, a recent study demonstrated that the expression of different pro-inflammatory cytokines, such as resistin and TNF α , augmented within 4 hours after coronary by-pass surgery in epicardial adipose tissue [59].

Adiponectin might also play a role in epicardial adipose tissue, as patients with advanced coronary heart disease have lower level of epicardial adiponectin, which potentially contributes to the increased cardiovascular risk [60].

4. Perivascular adipose tissue and atherosclerosis

Perivascular WAT (pWAT) is an appealing candidate for mediating at least in part the obesity-associated cardiovascular

risk. It is defined as the accumulation of adipocytes around vascular structures, and it can be found in the proximity of virtually all blood vessels, especially around the coronaries and the aorta, where its distance to the adventitia measures less than 0.1 mm. Conventionally, pWAT was considered to act largely as a structural support for blood vessels. However, recent data from epicardial adipose tissue and ex-vivo experiments with aorta and mesenteric arteries suggest that periaortic fat can modulate the vascular responsiveness to vasoactive agents [61–63]. In addition, we have recently shown that pWAT secretes a variety of cytokines and chemokines [64]. Consistent with this concept, feeding of a high-fat diet to rats augmented the amount of periaortic fat by 4 to 10 times in the abdominal aorta and iliac arteries, respectively [64]. Hence, an increase in pWAT and its local secretory activity could contribute to the pathogenesis and/or progression of obesity-induced hypertension and atherosclerosis (Fig. 4 and discussion below). Although the cytokines described below were all shown to be secreted by pWAT, only circumstantial evidence currently exists with regard to their direct pro-atherogenic action on the adjacent vasculature.

4.1. Production of chemokines and cytokines by pWAT

As the distance between pWAT and the vascular wall has been estimated to be less than 100 μm , it is easily conceivable that locally produced factors could interact with the vasculature. Consistent with this idea, we were able to demonstrate that human perivascular adipocytes are a source of cytokines, such as $\text{TNF}\alpha$, IL-1, IL-1Ra, IL-6, as well as chemokines like MCP-1, interleukin 8 (IL-8), interferon-(IFN)- γ -inducible protein (IP-10), and “regulated on activated normal T-cell expressed and secreted” (RANTES), all of which have been implicated in the progression of (or protection from) atherosclerosis [64].

4.1.1. $\text{TNF}\alpha$

$\text{TNF}\alpha$ is one of the most studied proinflammatory cytokines. Originally described to induce the necrosis of tumors after acute bacterial infections, it is now known to be involved in inflammatory diseases, tumorigenesis, metastasis, viral replication, septic shock and fever. Endotoxins, viruses, drugs and other cytokines (e.g. IL-1) can induce its production, whereas other cytokines (IFN α , IFN β or IL-6) are inhibitory [10]. $\text{TNF}\alpha$ is produced by a variety of different cell types ranging from cells of the immune system to tumor cells, fibroblast, smooth muscle cells, as well as epicardial and perivascular adipocytes [65,66]. $\text{TNF}\alpha$ has been linked to obesity in a murine model of obesity due to leptin-resistance (db/db mice), where epididymal adipose tissue was found to express $\text{TNF}\alpha$ at significant higher levels [67].

$\text{TNF}\alpha$ appears to play a certain role in insulin resistance, as it has the capacity to downregulate Glucose Transport Type 4 (GLUT4) in adipose tissue. Obese mice deficient in $\text{TNF}\alpha$ have lower glycemia and insulin levels, and they are more glucose tolerant than wild-type animals [50]. These

differences might be accounted for, at least partially, by a decrease in circulating free fatty acids, an increase of GLUT4 in muscle tissue, and an increase in the auto-phosphorylation of the insulin receptor in both adipose and muscle tissue.

$\text{TNF}\alpha$ secreted by perivascular adipocytes, could hence interact with the local vasculature by different mechanisms. First, $\text{TNF}\alpha$ could inhibit endothelial nitric oxide synthase (eNOS), therefore leading to the decreased production of nitric oxide (NO). Since NO is a potent vasodilator mediating e.g. the vasodilatory actions of insulin, a decrease in NO would result in an impairment in insulin-mediated vasodilatation, a reduction in muscle blood flow, thereby ultimately contributing to insulin resistance by limiting the substrate amount to the muscle [68].

4.1.2. $\text{TGF}\beta$

$\text{TGF}\beta$ is another cytokine found in WAT and produced by adipocytes. $\text{TGF}\beta$ restricts cell growth, differentiation and cell death and it has therefore been implicated as a regulator of tumor growth [69]. Similar to $\text{TNF}\alpha$, $\text{TGF}\beta$ also plays a role in adipose cell differentiation [70]. In addition, $\text{TNF}\alpha$ stimulates $\text{TGF}\beta$ synthesis, which in turn stimulates PAI-1 synthesis [71]. However, the precise role of $\text{TGF}\beta$ in atherosclerosis and its secretion by pWAT remains to be elucidated.

4.1.3. IL-1 and IL-1Ra

IL-1 is a family of three related cytokines (IL-1 α , IL-1 β and IL-1Ra), which are produced by distinct genes. IL-1 α and IL-1 β have undistinguishable pro-inflammatory actions on most cell types. IL-1 is mostly produced by stimulated monocytes and tissue macrophages, and it induces fever, the acute phase liver response, the proliferation of different cell types (fibroblasts, smooth muscle and mesangial cells) and the secretion of other cytokines. IL-1 has also pro-angiogenic actions and direct effects on adipocytes, where it increases lipolysis and impairs adipocyte differentiation through the inhibition of peroxisome proliferators-activated γ (PPAR γ), a nuclear receptor playing a major role in adipocyte differentiation [72].

The production of IL-1 by pWAT may therefore play a role in development of atherosclerotic lesions by promoting neoangiogenesis and smooth muscle cell proliferation, both of which are hallmarks of atherogenesis.

In contrast, IL-1Ra is unique by the fact that it is a specific natural antagonist of IL-1 and counteracts its pro-inflammatory actions by binding competitively to the IL-1 receptor without inducing a signal [73]. IL-1Ra is produced by monocytes, neutrophils, fibroblasts, and epithelial cells. Like IL-1, IL-1Ra is an acute-phase protein produced by liver cells in response to inflammatory stimuli; its secretion is modulated by other cytokines, such as IL-1, interleukin 3 (IL-3), interleukin 4 (IL-4), IL-10, $\text{TNF}\alpha$ and interferon β (IFN- β). It is now well known that IL-1Ra levels increase markedly in response to fever and inflammation acting as a host-defence mechanism [74]. Intriguingly, leptin, which is produced by

adipocytes and principally acts on energy homeostasis, induces the production of IL-1Ra by human monocytes, suggesting a putative anti-inflammatory action [75].

Although adipocytes produce IL-1Ra as well as IL-1, the levels of IL-1Ra are selectively and markedly elevated over 7-fold in the serum of obese patients [76]. While this up-regulation appears at first sight to be anti-inflammatory, and hence beneficial, recent data in rodents suggest that excess amounts of IL-1Ra lead to insulin resistance in skeletal muscle [77].

Since perivascular adipocytes secrete IL-1 and IL-1Ra [64], it can be hypothesized that these two cytokines play a modulating role in the development of atherosclerotic plaques, whereby IL-1Ra promotes the differentiation of adipocytes, as well as the proliferation of fibroblasts and smooth muscle cells.

4.1.4. IL-6

Together with IL-1 and TNF α , IL-6 provokes an acute phase reaction, such as fever and the hepatic production of acute phase proteins. IL-6, like IL-1Ra, also has some modulatory effects on inflammation: it decreases cytokines like TNF α and IFN γ and increases IL-1Ra [10]. Obesity is associated with increased IL-6 levels, whereas body weight loss results in a decrease [78]. IL-6 was shown to lead to a decrease in the insulin-dependent glucose uptake through the down-regulation of the expression of the insulin receptor substrate 1 (IRS-1) and GLUT4 [51]. In addition, IL-6 has central effects resulting in increased energy expenditure and in lower fat pad weight [79]. With regard to atherosclerosis, IL-6 could contribute to the local balance between pro- and anti-inflammatory cytokines in pWAT as well as on the proliferation of smooth muscle cells, and could also impair local insulin sensitivity by inhibiting IRS-1.

4.1.5. MCP-1

MCP-1, also called CCL2, belongs to the family of chemokines. The basal expression of MCP-1 is very low, but can be induced by many different stimuli, including cytokines (IL-1, TNF α) and endotoxins. Even more, MCP-1 mRNA is increased in obese mice, where the plasma levels correlate with body weight [80]. In humans, MCP-1 is produced by WAT and it was shown to impair insulin signaling in skeletal muscle cells at doses which correspond to the physiological plasma concentrations (200 pg/ml). Moreover, MCP-1 controls adipogenesis and triglycerides content of adipocytes, and it plays a role in adipocyte dedifferentiation through autocrine and paracrine mechanisms [81–83].

MCP-1 is a key mediator of monocyte trafficking and promotes macrophage recruitment, an essential step in atherogenesis, as its receptor (CCR2) is expressed on circulating monocytes, which in turn are important contributors to the progression of atherosclerosis [84].

MCP-1 is also produced by macrophages, endothelial cells and smooth muscle cells and is also secreted by epicardial WAT, as well as by pWAT; this is correlated with

the degree of infiltration of these WAT depots by inflammatory cells [58,64]. Immunohistochemical analysis clearly confirmed that adipocytes, rather than stromal cells, produce MCP-1 [64].

It has been shown that the local perfusion of MCP-1 after unilateral ligation of the femoral artery in apoE-deficient mice induced collateral blood flow in the hindlimb with an increase in perivascular monocytes and accelerated aortic plaque formation [85]. The atherogenic role of MCP-1 is further substantiated by the observation that mice lacking MCP-1 or its receptor (CCR2) exhibit a less severe pattern of atherosclerosis, with a reduction of plaque size and macrophage content [86,87].

In humans, the expression of CCR2 has been identified on smooth muscle cells and recent findings suggest that MCP-1 could also contribute to smooth muscle cell proliferation [88]. Moreover, MCP-1 has also systemic and paracrine actions on WAT, as it stimulates the secretion of leptin [83]. Leptin and MCP-1 are both angiogenic factors and contribute to formation of neo-vessels, which is an important component of atherosclerosis, where neo-vessels provide the necessary oxygen and nutrients for leukocyte accumulation.

Taken together, these data strongly suggest that MCP-1 contributes to chemotaxis, smooth muscle cells proliferation and neo-vessel formation; hence, the local production of this chemokine in the immediate vicinity of the vascular wall is likely to have an impact on the biology of atheromatous lesions.

4.1.6. IL-8

IL-8 (or CXCL-8) is another chemokine involved in atherogenesis. IL-8 is derived from many different cells, including monocytes, lymphocytes, granulocytes, fibroblasts, endothelial cells, bronchial epithelial cells, keratinocytes, hepatocytes, mesangial cells and chondrocytes. IL-1 β and TNF α increase IL-8 release, whereas dexamethasone and IFN β are inhibitory [89]. IL-8 is not only chemotactic for monocytes, but also for numerous other cell types, including neutrophils, T-cells, basophils and smooth muscle cells.

Different studies have confirmed that IL-8 plays a role in mediating the arrest of monocytes on endothelial cells, a key step in the mechanism of the infiltration of the vascular wall by leukocytes [90,91]. The IL-8 receptor (CXCR2) is strongly expressed in macrophages within atherosclerotic lesions. Consistent with these findings, mice lacking CXCR2 showed a significant reduction in atherosclerotic lesions and leukocyte accumulation [92]. In humans, IL-8 could contribute to obesity related low-grade inflammatory state, as IL-8 is increased in obesity [93]. However, the action of IL-8 is not limited to acute inflammation, as it stimulates the proliferation of endothelial cells and has potent angiogenic actions [94].

Since we have demonstrated that adipocytes from pWAT secrete significant amounts of IL-8 [64], it is quite plausible that this factor might locally contribute to atherosclerosis. However, direct mechanistic evidence linking pWAT to atherogenesis (e.g. by examining the impact of a pWAT-

selective gene ablation of IL-1 or MCP-1 in an atherosclerosis prone animal model) is currently lacking.

4.1.7. IP-10

IP-10 (or CXCL-10) is produced by many different cell types after stimulation by IFN or lipopolysaccharides, including endothelial cells, keratinocytes, monocytes, respiratory and intestinal epithelial cells and smooth muscle cells. In WAT, it is regulated *ex vivo* by IFN- β , and *in vivo* by inflammatory conditions such as obesity, atherosclerosis and diabetes (E. Henrichot, C.A. Meier, unpublished data). Furthermore, IP-10 is also secreted by pWAT and it contributes to the chemotaxis of white blood cells, smooth muscle cells migration and neo-angiogenesis. IP-10 is chemoattractive for lymphocytes and monocytes, and it induces the proliferation and migration of smooth muscle cells from the media to the intima [95].

4.1.8. RANTES

The “regulated on activated normal T-cell expressed and secreted” chemokine (RANTES) or CCL5 is another potential candidate implicated in atherosclerosis. RANTES is chemotactic to T-lymphocytes and macrophages and decreases the amount of collagen production. It is secreted by numerous cells including endothelial cells, smooth muscle cells, activated T-cells, macrophages and platelets, and has been implicated in cardiovascular inflammation after organ transplantation or arterial injury. In patients with endstage renal disease and type 2 diabetes, polymorphisms of the RANTES gene were associated with increased mortality [96]. Veillard et al. showed that antagonism of RANTES receptor reduced atherosclerotic plaque formation in mice [97].

Human subcutaneous WAT and pWAT both produce RANTES, and this production is upregulated by systemic inflammatory cytokines such as IFN- β and IL-1 (E. Henrichot, C.A. Meier, unpublished data).

4.2. Role of extracellular matrix and metalloproteinases

One of the first steps in angiogenesis is the breakdown of the subendothelial basement membrane and the surrounding extracellular matrix (ECM). This is followed by endothelial cell migration and proliferation. Metalloproteinases (MMPs) are a large family of zinc-dependent proteinases, which digest various components of the ECM, thereby stimulating the migration and attachment of endothelial cells [98]. Besides this function, MMPs also play a role in the differentiation of adipocytes [99]. The action of MMPs is inhibited by endogenous inhibitors, such as the tissue inhibitor of metalloproteinases (TIMPs). Regional disturbance in the balance of MMPs and TIMPs could contribute to the vulnerability of the plaque and/or vascular remodeling. Indeed, it has been shown that oxidized lipids upregulate MMP-9 and downregulate TIMP-1 in human macrophages [100]. Moreover, IL-8 downregulates TIMP-1

expression in human atherosclerotic lesions, thereby possibly contributing to the development of atherosclerotic lesions [101].

Recent studies have shown that human adipocytes produce MMP-2 and MMP-9 with a diminution of TIMP-1 [102]. These findings suggest that adipose tissue might promote the development of new vessels. Leptin, which is also secreted by adipocytes, could also act to promote neovascularisation by promoting the expression of MMPs as shown in a rat corneal model [103]. Consistent with this, leptin is capable of inducing the proliferation of human umbilical endothelial cells and increases MMPs in a dose-dependent manner, contributing to the development of neovessels [103]. Taken together, WAT secretes several key components required for neoangiogenesis, which is in turn a proatherogenic process.

4.3. Role of angiogenesis

Angiogenesis plays an important role in tumor growth, but also in atherogenesis. As mentioned above, blood vessels

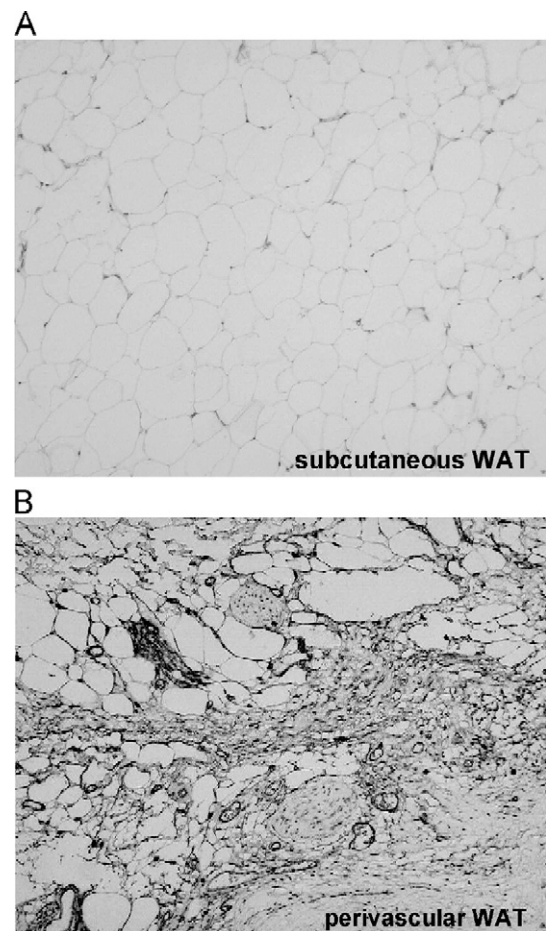


Fig. 3. Perivascular adipose tissue is characterized by increased angiogenesis as compared to subcutaneous WAT. Immunohistological staining of endothelial cells (CD34+) in human WAT: subcutaneous WAT (panel A) and pWAT (panel B). Courtesy of C. Juge-Aubry and C.A. Meier.

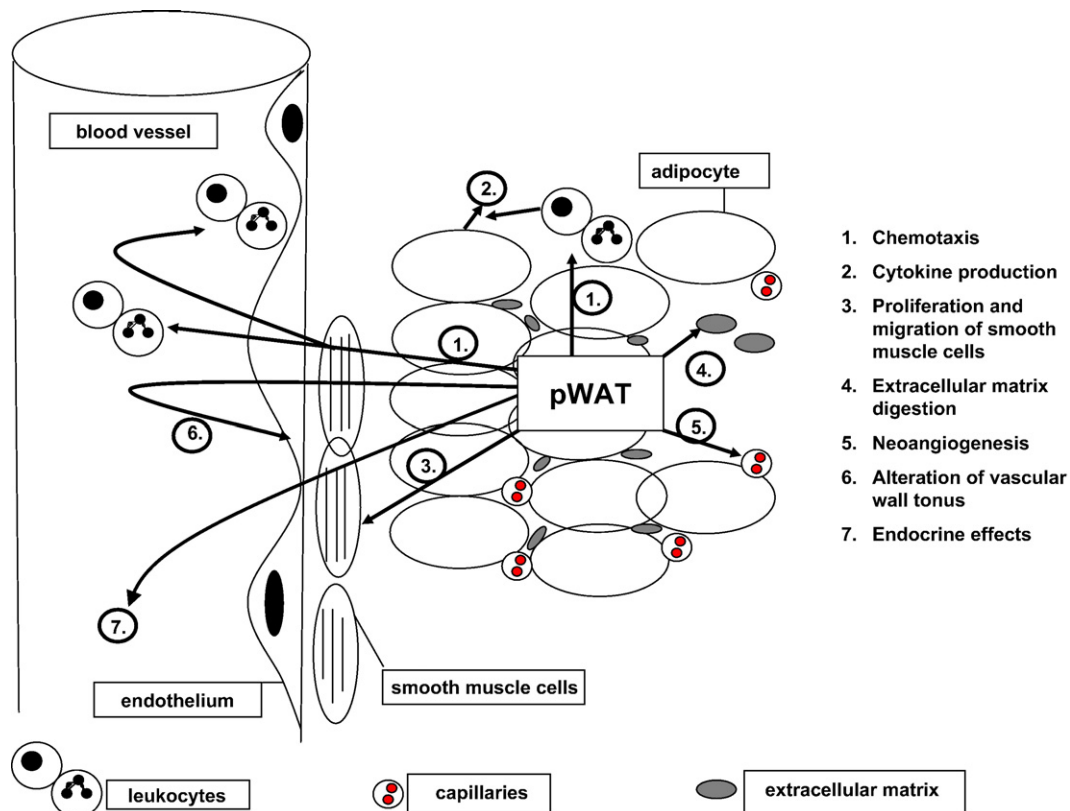


Fig. 4. Hypotheses linking pWAT to atherosclerosis. Arrow 1: chemoattraction of leukocyte by MCP-1, IP-10, RANTES and IL-8 (produced by perivascular adipocytes) and adhesion to endothelial cells. Arrow 2: production of pro- and anti-inflammatory cytokines such as $\text{TNF}\alpha$, IL-8, IL-6, IL-1 and IL-1Ra by adipocytes. These factors contribute to a local inflammatory burst with tissue remodelling, macrophage activation and enhanced chemoattraction of leukocytes. Arrow 3: MCP-1, IP-10 and IL-6 stimulate the migration and proliferation of smooth muscle cells. Arrow 4: Extracellular matrix is digested by MMPs secreted by adipocytes, which is the first step in the formation of neo-vessels. Arrow 5: Angiogenin, leptin and MCP-1 stimulate neo-angiogenesis. This allows oxygen and nutrition delivery and apperas to contribute to plaque development. Arrow 6: Reactive oxygen species, $\text{TNF}\alpha$ and possibly angiotensin II interact with NO bioavailability, thereby leading to vasoconstriction. Arrow 7: Adiponectine, visfatin, resistin, leptin, $\text{TNF}\alpha$ and other cytokines also enter the systemic circulation and act centrally on food intake and body weight.

are necessary for plaque formation, as they provide the necessary oxygen and nutrients, but also a vascular network for inflammatory cells [104]. Intriguingly, the fat deposits in obesity are characterized by an expansion of the capillary bed (E. Henrichot, C.A. Meier, unpublished data). Furthermore, human WAT is a source of many angiogenic factors, such as IL-6 and IL-8, MCP-1, leptin, fibroblast growth factor and vascular endothelial growth factor. As illustrated in Fig. 3, neoangiogenesis was more pronounced in pWAT as compared to subcutaneous WAT.

Specifically, we have shown that pWAT produces significant amounts of angiogenin, which belongs to the family of pro-angiogenic factors. Angiogenin promotes the invasiveness and proliferation of cultured endothelial cells, and also serves as an adhesion molecule for endothelial cells. Indeed, primary adipocytes from pWAT induced the formation of capillary-like structures when co-cultured with aortic bovine endothelial cells; the addition of RNasin, an inhibitor of angiogenin, entirely abolished the formation of capillary tubes (E. Henrichot, C.A. Meier, unpublished data). Hence, the secretion of angiogenic factors by pWAT

appears to be sufficient to induce angiogenesis in adjacent structures.

4.4. Role of adipose tissue derived oxidative stress

Obesity is characterized by a systemic increase in oxidative stress [105]. Subcutaneous adipose tissue from obese subjects produces more reactive oxygen species, contributing to the augmented oxidative stress in obesity [106]. The augmented oxidative stress plays a role in vascular tone, since a recent study has shown that pWAT enhances the arterial contractile response to perivascular nerve stimulation cells through the production of superoxide [107].

4.5. Increased arterial wall stiffness and vascular reactivity

Soltis and Cassis demonstrated in 1991 that pWAT significantly modifies the vascular response of aortic rings to norepinephrine in vitro [62]. More recently, another factor derived from pWAT, named adventitium derived relaxing factor (ADRF), which is NO-independent, but calcium

dependent, was described, but its precise nature remains elusive [61].

It is well known that angiotensinogen and angiotensin-converting enzymes alter vascular tone and the circulating levels of angiotensinogen and angiotensin II are increased in human obesity [108]. Angiotensin II leads not only to vasoconstriction, but also induces the endothelial production of MCP-1, intracellular adhesion molecule-1 and vascular adhesion molecule-1 [109]. Angiotensin II also interacts with NO metabolism by enhancing the formation of oxygen free radicals, which may damage vascular tissue. NO is not only a potent vasodilator, but also protects the wall by inhibiting the adhesion of monocytes and by decreasing vascular smooth muscle cell proliferation [11].

pWAT may also have a direct mechanical impact on the vasculature. Young obese subjects have an increased vascular stiffness [110,111] which can be reduced by weight loss, as measured by Doppler ultrasound [112]. Arterial stiffness could well be related to excess vascular rigidity caused by accumulation of periaortic fat deposits, but also to sympathetic overactivity found in obesity [113]. In stiffer vessels the Windkessel effect is ineffective and therefore, reflection waves travel more quickly to the heart leading to an increase in blood pressure during systole.

Obesity-induced hypertension is frequent, as up to 50% of obese individuals have concomitant hypertension; the pWAT-related mechanisms detailed above could all potentially contribute to the pathogenesis of obesity-induced hypertension.

5. Conclusion

As obesity develops, WAT mass increases together with its secretory activity. Adipose tissue can be found in many different localisations in human body and its effects are local or systemic. Therefore, it is a very appealing concept that pWAT, which produces key molecules in inflammation and chemotaxis, contributes to obesity-associated atherosclerosis and hypertension (Fig. 4).

As obesity develops, there is hypertrophy and hyperplasia of perivascular adipocytes. $\text{TNF}\alpha$, $\text{TGF}\beta$, IL-8, IL-6, IL-1 and IL-1Ra and chemokines like IP-10, MCP-1 or RANTES are all secreted by pWAT. These peptides contribute to the chemotaxis of leukocytes to the vascular endothelium and their migration into the vascular wall. The consequence is a local inflammatory burst with production of additional cytokines and chemokines by chemo-attracted leukocytes and adipocytes. The local production of MMPs, as well as of various angiogenic factors by WAT increases neo-vascularisation, which in turn supplies the oxygen and nutrients necessary for the maintenance and development of local inflammation and plaque formation. Some pWAT-derived chemokines, such as MCP-1 and IP-10, stimulate the migration and proliferation of smooth muscle cells.

Finally, angiotensin II and $\text{TNF}\alpha$, together with the local overproduction of reactive oxygen species, contribute to a

lower bioavailability of NO, putatively leading to vasoconstriction and impaired insulin-mediated vasodilatation, thereby ultimately enhancing insulin resistance.

Taken together, pWAT has all the characteristics of a local promoter of atherosclerosis. However, this appealing concept requires confirmation by further mechanistic research and intervention trials. Although the direct causal role of pWAT in the process of atherogenesis will be challenging to establish, it might potentially provide a novel target for the prevention and treatment of obesity-associated cardiovascular complications.

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